AMENDMENTS TO THE SPECIFICATION

Please replace the paragraphs at page 5, lines 10-21 of the specification with the following:

The term Annexin V is well know to those skilled in the art and is used, for example, in documents cited above, for example, EP 1 379 266, incorporated herein by reference. As will be apparent to the skilled person, the N-terminal fragment of Annexin V is large enough to be recognisable by the skilled person as a fragment of Annexin V (rather than, for example, a fragment of another annexin).

The pharmaceutical composition may comprise an effective amount of the Annexin V protein or N-terminal fragment of Annexin V, optionally in combination with a carrier and additives. Suitable carriers and additives which can be used will be well known to those skilled in the art, including the examples used in EP 1 379 266, incorporated herein by reference. The salt can be a pharmaceutically acceptable acid addition salt where the counter ion is, for example, chloride, acetate.

Please insert the following text at page 5, line 15 of the specification (*i.e.*, between the two paragraphs amended above):

Annexins can be purified from human tissues or produced by recombinant technology. For instance, annexin V can be purified from human placentas as described by Funakoshi et al. (1987). Examples of recombinant products are the expression of annexin V in *Escherichia coli* (Kang, H.-M., Trends Cardiovasc. Med. 9: 92-102 (1999); Thiagarajan and Benedict, 1997, 2000). A rapid and efficient purification method for recombinant annexin V, based on Ca^{2+}-enhanced binding to phosphatidylserine-containing liposomes and subsequent elution by EDTA, has been described by Berger, FEBS Lett. 329: 25-28

(1993). This procedure can be improved by the use of phosphatidylserine coupled to a solid phase support.

Accordingly, in another embodiment of the invention, the modified annexin V protein is a polymer of annexin V that has an increased effective size. It is believed that the increase in effective size results in prolonged half-life in the vascular compartment and prolonged antithrombitic activity. One such modified annexin is a dimer of annexin V. A homodimer of annexin V can be produced using a DNA construct as described in Example 1 of EP 1 379 266, the contents of which are incorporated herein by reference.

Please insert the following text at page 5, line 22 of the specification (*i.e.*, following the second of the two paragraphs amended above):

In one embodiment, the present invention provides an isolated modified annexin V, coupled to polyethylene glycol (PEG). Preferably, at least two PEG chains are coupled to a single annexin molecule, with each PEG having a molecular weight of at least 5 kDa, more preferably at least 10 kDa, and most preferably at least 15 kDa. In an alternative embodiment, an isolated modified annexin protein contains an annexin protein coupled to at least one additional protein, such as an additional annexin protein (forming a homodimer) or the Fc portion of immunoglobulin. The additional protein preferably has a molecular weight of at least 30 kDa.

Annexins can be coupled to polyethylene glycol (PEG) by any of several well-established procedures (reviewed by Hermanson, 1996) in a process referred to as pegylation. The present invention includes chemically-derivatized annexin molecules having mono-or poly- (e.g., 2-4) PEG moieties. Methods for preparing a pegylated annexin generally include the steps of (a) reacting the annexin with polyethylene glycol (such as a reactive ester or aldehyde derivative of PEG) under conditions whereby the annexin becomes attached to one or more PEG groups and (b) obtaining the reaction product or products. In general, the optimal reaction conditions for the reactions must be

determined case by case based on known parameters and the desired result. Furthermore, the reaction may produce different products having a different number of PEG chains, and further purification may be needed to obtain the desired product.

Conjugation of PEG to annexin V can be performed using the EDC plus sulfo- NHS procedure. EDC (1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride) is used to form active ester groups with carboxylate groups using sulfo-NHS (N-hydroxysulfosuccinamide). This increases the stability of the active intermediate, which reacts with an amine to give a stable amide linkage. The conjugation can be carried out as described in Hermanson, 1996.

Bioconjugate methods can be used to produce homopolymers or heteropolymers of annexin; methods are reviewed by Hermanson, 1996. Recombinant methods can also be used to produce fusion proteins, e.g., annexin expressed with the Fc portion of immunoglobulin or another protein. All of these procedures increase the molecular weight of annexin and have the potential to increase the half-life of annexin in the circulation and prolong its anticoagulant effect.